Title: Health state utility values for age-related macular degeneration: review and advice

Short title: Health state utility values for AMD

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Abstract

Health state utility values are a major source of uncertainty in economic evaluations of interventions for age-related macular degeneration (AMD). This review identifies and critiques published utility values and methods for eliciting de-novo utility values in AMD. We describe how utility values have been used in health care decision making and provide guidance on the choice of utility values for future economic evaluations for AMD. Literature was searched using PubMed and health technology assessments (HTA) were searched using HTA agency websites to identify articles reporting utility values or approaches to derive utility values in AMD and articles applying utility values for use in health care decision making.*s*71 studies qualified for data extraction of which 22 were classified as containing utility values and/or elicitation methods relevant to AMD, while 49 were classified as using utility values in decision-making. A large number of studies have elicited utility values for AMD, although those applied to decision making have focused on a few of these. There is an appreciation of the challenges in the measurement and valuation of health states, with recent studies addressing challenges such as the insensitivity of generic health-related quality of life (HRQoL) questionnaires and utility in the worse seeing eye. We would encourage careful consideration when choosing utility values in decision making and an explicit critique of their applicability to the decision problem.

Key Points for Decision Makers:

- There is a large body of literature describing utility values in AMD.
- Challenges for estimating utilities in AMD include the insensitivity of generic HRQoL questionnaires and valuing vision in the worse seeing eye.
- Economic evaluations of interventions for AMD have relied on a small number of utility studies, which may not meet some important criteria.

1. Background

Age-related macular degeneration (AMD) is a common cause of visual impairment in older adults. Untreated, the disease leads to the progressive loss of central vision and impacts on ability to perform daily activities such as recognising faces and reading.[1]

The disease covers two forms with different underlying causes: Dry AMD begins with drusen in the macular (age-related maculopathy) which may develop into geographic atrophy. There is currently no treatment for dry AMD. Wet (neovascular) AMD is caused by abnormal blood vessel growth. A number of treatments have become available for neovascular AMD over the past 10 years: firstly verteporfin photodynamic therapy (vPDT), and later a number of anti-vascular endothelial growth factors (anti-VEGFs) including ranibizumab (Lucentis), bevacizumab (Avastin) and aflibercept (Eylea), stimulating interest in the incremental value of these new treatments over the standard of care.

Cost-utility analysis has been widely used to assess relative value of these interventions. A recent review of economic models comparing treatments for AMD identified 36 studies of which all but 3 reported costs per quality-adjusted life year (QALY).[2]

QALYs are calculated by weighting each year of life lived using a utility score. Utility scores are anchored so that 1 is perfect health and 0 is equivalent to the state of death. Multiplying time in a health state by the health state utility value, 1 year of life lived in perfect health is equal to 1 QALY.[3]The term 'utility' in cost-utility analysis and its theory is based on von Neumann-Morgenstern (vN-M) utility theory. The normative model for utility theory, the model for how a rational individual ought to behave, is that utility scores represent the strength of an individual's preference when faced with uncertainty for a given outcome, in this case a health state.[4]

Within economic models, utilities have been identified as major sources of uncertainty: both in terms of the sensitivity of model outputs to the choice of utility values and in terms of the methods by which utility values are elicited.[2]

The importance of utility values in economic evaluations of interventions for AMD stems from the nature of the condition: the disease is characterised by the progressive loss of central vision, which severely limits the ability to perform daily activities and consequently has a major impact on quality of life. There have been two relevant reviews to date covering utility values in AMD. *Pearson et al.* systematically reviewed utility values specific to wet AMD and evaluated these against the NICE reference case. [5] They recommended the time trade-off (TTO) and Health Utilities Index Mark 3 (HUI3) for use in economic evaluations based on the correlation of these measures with visual acuity. *Poku et al.* systematically reviewed articles reporting the relationship between visual acuity and utility across AMD, diabetic retinopathy (DR) and diabetic macular oedema (DMO).[6] They found that self-reported time trade-off was most strongly associated with visual acuity and that utility values had a higher association with the better seeing eye than the worse seeing eye.

Also of note, *Tosh et al.* reviewed generic preference-based measures of health-related quality of life (HRQoL) in visual disorders, finding that the performance of the EQ-5D was mixed, and that more head to head comparisons were needed between the EQ-5D, the SF-6D and the HUI-3.[7]

This review aims to identify and critique published utility values and methods for eliciting de-novo utility values in AMD. The review describes how utility values have been used in economic models and health care decision making and provides guidance to the choice of utility values for future economic evaluations for AMD.

2. Methods

A search was conducted in PubMed to determine what approaches have been used to derive utility values in AMD and how utility values have been used in health care decision making. The search was supplemented with HTA agency websites to support the latter aim.

Title and abstracts were searched in PubMed on 3 January 2016. No date or language restrictions were applied to the searches. Terms covering AMD and utility were combined using the following search strategy:

[(macular degeneration) OR (geographic atrophy)] AND [(qaly) OR (quality-adjusted life year) OR (utility)]

Key HTA agency websites (UK: National Institute of Health and Care Excellence (NICE), Sweden: Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), Australia: Medical Services Advisory Committee (MSAC), Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)) were searched for technology appraisals in English language covering interventions for macular degeneration.

A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) scheme (***Table 1***) illustrates the included studies after title/abstract and full text reviews. Of the 206 studies identified, 113 studies were excluded after review of abstracts and titles. Reasons for exclusion included the topic not relating to utility, the disease not covering AMD, there being no primary data (e.g. letter or review) and the language not being English. After full text review, a further 23 studies were excluded due to the topic not relating to utility, the type of article being a letter or review with no primary data, or the study being a duplicate.

Included studies were classified by those reporting utilities (utility sets or methods to derive utility sets) and by those applying utilities to decision making (economic evaluations and HTAs). Two data extraction sheets were used to classify the data from the studies. In the first extraction sheet key

methodological parameters such as elicitation technique, geography and sample were recorded for studies reporting utility sets or methods to derive utility sets. In the second extraction sheet utility values used in the base case were recorded for economic evaluations and HTAs.

3. Results

70 studies were selected for data extraction of which 22 were classified as containing utility values and/or elicitation methods relevant to AMD, while 48 were classified as using utility values in decision-making. A small number of the latter also collected de novo utilities. ***Table 2*** and ***Table 3*** summarise the key components of the included studies.

1. Utility values and elicitation methods

The majority of utility values identified were classified by health states. This is likely due to the majority of economic models for AMD being health state transition models. The health states tend to be defined by visual function parameters, chiefly visual acuity, although contrast sensitivity has also been associated with utility and research has suggested that contrast sensitivity may be better correlated with utility than visual acuity.[8, 9]

Early studies focused on the elicitation of utilities directly from patients. For example, *Brown et al.* elicited utilities from patients using the TTO and SG.[10] Utilities have also been elicited via tariffs of preference-based questionnaires,[8] from healthy volunteers via simulation contact lenses[11] and from ophthalmologists.[12]

The most common elicitation method was the TTO, which was used in 16 of the 22 studies. Anchors of perfect health/ death and perfect vision/ blindness have been used to elicit utilities. (**Table 2**) It has been shown that different utility values can be obtained depending on the anchor. For example, *Au Eong et al.* obtained a mean utility of 0.91 using the standard gamble (SG) anchored to blindness and 0.86 using the SG anchored to death.[13]

Samples for deriving utility estimates ranged in size depending on the research question, with the largest being a 1,829 AMD patients who completed the SF-36 as part of the Verteporfin Photodynamic Therapy Cohort Study.[14] (**Table 2**)

Utilities are available for a number of countries (**Table 2**). The USA and the UK were the most common countries for utilities, which is indicative of the location of prominent health economic research groups, but may also be a function of an English language search strategy.

Lee et al. found considerable variation in the utility values reported, with values differing by as much as two-fold between studies.[15] A number of studies used several methods and presented different utility values by method, with several studies making the differences between elicitation methods a particular focus. *Yanagi et al.* found that TTO-derived utilities correlated more strongly with better seeing eye VA than SG-derived utilities in a study of Japanese patients.[16] *Stein et al.* investigated the impact of eliciting utilities for AMD health states from different groups. They found that patients rated their health more severely than clinicians or the general population using the TTO.[17]

Some studies highlighted the challenges of using generic preference-based questionnaires to derive utilities in AMD and proposed recommendations and/or methodological improvements. *Espallargues et al.* elicited utilities for several generic preference based questionnaires and the TTO, concluding that the HUI-3 would be the preferred measure.[8] One study provided a mapping algorithm to derive utilities from the NEI-VFQ-25. *Payakachat et al.* predicted EQ-5D utility values from the NEI-VFQ 25 in a population of patients with wet AMD.[18]

The multi-factorial considerations of utility in AMD have been addressed by a number of papers. Most utility values were associated with the better seeing eye. Utility values can vary considerably depending on whether the better seeing or worse seeing eye is affected and utility values for the worse seeing eye are available.[19] *Skalicky et al.* investigated the impact of ocular comorbidities on utility, chiefly AMD in glaucoma patients.[20] While adverse events have been elicited including event-based utility decrements. For example *Mowatt et al.* applied utility weights based on *Brown et al.* for health states and then decrements for adverse events including cataract, endophthalmitis, retinal detachment and uveitis.[21]

2. Utility values in decision making

All but one of the studies identified in this review that applied utilities to decision making took the form of cost-utility analyses. One study compared QALYs without including costs: *Kim et al.* investigated the impact of PDT on AMD patients in Korea.[22]

Most studies applied utilities from *Brown et al.* based on TTO in a sample of AMD patients.[10] (**Table 3**) These utility values were derived from a mixed population of wet and dry AMD, whereas the decision problem of many papers was often for a specific form of AMD. Studies assessed a number of treatments including anti-VEGFs, PDT and screening, although there was no trend to apply different utility weights based on the intervention under consideration. Neither was there a trend to apply different utility values by geography of study, despite values being available for several geographies.

Studies found that the choice of utility set could result in very different estimated QALY gains for similar decision problems. *Kymes et al.* estimated an incremental QALY gain of 1.15 for ranibizumab or bevacizumab for AMD in their report for CADTH[23] compared with NICE's estimates of incremental QALYs of 0.45 to 0.73, depending upon the scenario.[24] They concluded that the likely reason for the difference was the utility sets used (*Espallargues et al.* for NICE and *Sharma et al.* for CADTH), although the two models varied in other inputs too.[8, 25]

3. Discussion

Utility values have been widely used in decision making in AMD and the choice of utility values has been frequently highlighted as having a major impact on the results of economic evaluations.

These evaluations have focused on a few utility sets[10] while other utility sets have not been used to date[18]. Such a focus on a limited range of utility sets improves comparability between studies, although the trade-off is to accept the limitations of the utility values used in terms of methodology and sample.

The most frequently used utility values from *Brown et al.* were derived for visual acuity health states from a mixed sample of wet and dry AMD patients in the USA.[10] While many economic models focused on specific forms of AMD (wet in the case of evaluations of anti-VEGF therapies) and covered different geographies, most economic models applied the utility values from this small sample of US patients with wet and dry AMD.

Some papers sought to provide guidance on utility values although there is little evidence that this has been followed. Notably *Espallargues et al.* concluded that the HUI-3 would be preferred for use in economic evaluation due to its stronger correlation with visual acuity and contrast sensitivity.[8] However, the HUI-3 was rarely used by studies since (or prior to) this publication.

Some articles that contain relevant guidance on utility values in AMD may not have been picked up by the search strategy if they did not mention the condition explicitly. For example, in an attempt to address the insensitivity of generic HRQoL questionnaires in vision disorders, a vision 'bolt-on' was developed for the EQ-5D 3L.[26] The EQ-5D+V has been valued in the general population, although the questionnaire content is yet to be validated in patients with vision disorders. The focus of this review was utility values for AMD, therefore it did not include articles on other vision disorders, although many of the findings can be applied to vision disorders more broadly.

What makes 'good' utility values? The strength of utility values depends on the context of use. However a few general guidelines can be given for choosing utility values for any condition and a few more specific guidelines can be given for AMD.

Generally, the choice of utility value should reflect the perspective of the decision problem. For example, decisions concerning publically funded health care systems should apply utility values that are representative of the preferences of the general population.[27] Utility values are known to vary by geography, so where possible, preferences should reflect the geography of the decision problem. The measurement of health states on which the utility values are based should be based on the patient-reported health of subjects who are experiencing the health state in question.

For AMD there is are a number of utility values available that meet the needs of different geographies and various health states as defined by type of disease (wet or dry AMD) and by levels of visual function. There remain a number of issues that are specific to AMD that should be considered when interpreting or applying utility values:

1. *Adaptation*

For chronic conditions, the concept of adaptation exists, whereby patients may adapt to their condition and therefore rate their health state less severely than a member of the community who is unaffected by the condition.[28]

In AMD patients there is evidence that patients rate their health state more severely than the public or their clinicians, which would run contrary to the theory of adaptation.[17] For these reasons, we urge careful consideration of the choice of patient or general public utility values and note that this will be further influenced by the perspective of the evaluation.

2. *Age and co-morbidities*

Utility values should be collected on a scale anchored by perfect health and dead.[3] AMD tends to affect older people who may be experiencing one or more other diseases and the impact of co-

morbidities makes the interpretation of absolute utility values challenging. While cost-utility analysis requires only the change in utility over time, comorbidities may increase the variability in utilities collected and so require larger sample sizes to collect robust utility sets.

3. *Better or worse seeing eye*

Whether the presenting eye is the better or worse-seeing eye is a significant determinant of the impact of the disease on a patient's quality of life. AMD in the better seeing eye has a greater impact on a patient than AMD in the worse seeing eye, although vision in both eyes can have an independent impact, and this is reflected in the utility values for each eye.[29] Utility values should incorporate the impact of the disease on the patient's daily life, so should account for vision in both eyes and their interaction.

4. *Wet/ dry AMD*

Utility values are available for samples of wet AMD, dry AMD and mixed samples. Generally the most appropriate utility set will be that which matches the condition in the decision problem. Most, but not all, decision problems have related to treatments for wet AMD due to the emergence of anti-VEGF therapies and therefore it would have been expected that utility sets using a wet AMD population would have been used most frequently. However, the most frequently used utility sets were from a mixed sample.[10]

5. *Visual function*

Most economic models are based on visual function, with visual acuity being the most common measure. Utility values are most frequently available for visual acuity. Utility values are also available for contrast sensitivity, although the potential to use these in economic evaluation is limited by the lack of outcomes data collected on the parameter in trials or routine practice. The choice of visual function parameter should be driven by an understanding of the association between visual function and utility as well as the availability of that parameter in the dataset of interest.

5. Conclusion

There is a large body of literature describing utility values in AMD. An appreciation of the challenges in the measurement and valuation of health states is evident from the papers identified in this review, with recent studies addressing challenges such as the insensitivity of generic HRQoL questionnaires and utility in the worse seeing eye. However, the use of utility values in decision making has seemingly not kept pace with these methodological developments with a reliance on a small number of utility studies.

The choice of utility value should be based on a number of considerations, some positive and others normative. It is unlikely that all can be fully addressed by one utility set, therefore we would encourage careful consideration when choosing utility values in decision making, an explicit critique of their applicability to the decision problem and the impact of alternative utility sets should be presented within sensitivity analysis.

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Tables

Table 1: PRISMA scheme

Stage	PubMed	HTA websites
Articles identified in search	199	7
	Included = 206	
Level 1: Title and abstract review	Excluded = 113. Reason: Topic not utility (84), Disease not macular degeneration (15), Review/letter (3), Language not English (10) Included = 93	
Level 2: Full text review	Excluded = 23. Reason: Topic not utility (6), Review/letter (12), Duplicate (5) Included = 70	
Articles included in review	Utility/methods = 22 Decision-making = 48	

Table 2: Utility values or methodological studies

Reference*	Valuation technique	Population	Sample size	Geography	Associations
Skalicky et al.[20]	Visual Function Questionnaire Utility Index	Glaucoma patients with AMD	200 glaucoma patients of which 73 had AMD	United Kingdom	N/A
Butt et al.[30]	N/A	Healthy volunteers	5	United Kingdom	N/A
Butt et al.[31]	EQ-5D, SF-6D, TTO, VAS	Patients with AMD	60	United Kingdom	BSE VA
Finger et al.[19]	EQ-5D, TTO, SG, VAS	Patients with nAMD	55	Germany	BSE VA, WSE VA
Au Eong et al.[13]	EQ-5D, TTO, SG	Patients with AMD	338	Singapore	BSE VA, WSE VA, weighted average of both eyes VA
Yanagi et al.[16]	TTO, SG	Patients with bilateral exudative AMD	48	Japan	BSE VA
Reeves et al.[14]	SF-6D	Patients with nAMD	1829	United Kingdom	VA, CS
Payakachat et al.[18]	Mapping to EQ-5D	Patients with wet AMD	151	Australia, the Netherlands, United Kingdom, United States	NEI VFQ-25
Czoski-Murray et al.[11]	TTO for simulated health states	Healthy volunteers	108	United Kingdom	BSE VA

Real et al.[32]	TTO	Patients with AMD, DR, retinal tear, retinal vascular obstruction, uveitis, macular oedema, macular pucker, other	51 AMD	United States	N/A
Lee et al.[15]	SG	Patients with AMD, DR, glaucoma, cataract or refractive error	44 AMD	United States	BSE VA
Sahel et al.[29]	HUI-3	Patients with wet AMD	360	France, Germany, Italy	BSE VA, WSE VA
Aspinall et al.[33]	TTO, conjoint analysis	Patients with AMD	122	United Kingdom	Binocular VA, binocular CS, AMD grade
Bansback et al.[9]	HUI-3, TTO	Patients with AMD	209	United Kingdom	BSE VA, WSE VA, binocular VA, binocular CS
Brown et al.[34]	TTO	Patients with AMD, public, clinicians and ophthalmologists	82 patients, 142 community, 62 clinicians, 46 ophthalmologists	United States	BSE VA
Espallargues et al.[8]	EQ-5D, SF-6D, HUI-3, VAS, TTO	Patients with AMD	209	United Kingdom	BSE VA, Binocular CS, VF-14
Stein et al.[17]	TTO	Patients with AMD, healthy volunteers, clinicians	115 patients, 142 volunteers, 62 clinicians	United States	BSE VA
Brown et al.[35]	TTO	Patients with AMD or DR	246 AMD	United States	BSE VA
Hollands et al.[36]	TTO	Patients with DR and AMD	14 AMD	Canada	N/A
Sharma et al.[25]	TTO	Patients with ocular conditions, including macular degeneration, cataract, glaucoma and diabetic retinopathy	239	United States	BSE VA
Brown et al.[12]	TTO, SG	Ophthalmologists	46	United States	BSE VA
Brown et	TTO, SG	Patients with	80	United	BSE VA

al.[10]		AMD		States	

TTO = time trade-off, SG = standard gamble, VAS = visual analogue scale, VA = visual acuity, CS = contrast sensitivity, BSE = better seeing eye, WSE = worse seeing eye. *ordered by year of publication.

Table 3: Utility values used in decision making

Reference*	Intervention	Country	Utility values
Ma et al.[37]	Cataract surgery in advanced AMD	China	Within study (T
Chan et al.[38]	Screening for intermediate AMD during DR screening	Hong Kong	Brown 2005, as
Butt et al.[39]	Ranibizumab for AMD	United Kingdom	Brown 2000[10]
Tamura et al.[40]	Screening for AMD	Japan	Brown 1999, Br 2000[10]
Mowatt et al.[21]	OCT for diagnosis, monitoring and treatment decisions in AMD	United Kingdom	Brown 2000[10] 2007
Dakin et al.[41]	Ranibizumab and bevacizumab for AMD	United Kingdom	Within study (E
Elshout et al.[42]	Aflibercept for AMD	Netherlands	Within study (H
Butt et al.[43]	Bevacizumab for AMD	United Kingdom	Espallargues 20
Stein et al.[44]	Bevacizumab and ranibizumab for newly diagnosed AMD	United States	HS: Brown, Side Aaberg, Bajaj, B Freeman
Reeves et al.[14]	Verteporfin PDT for AMD	United Kingdom	Within study (SI
Athanasakis et al.[45]	Ranibizumab for AMD	Greece	Brown 2000[10]
Brown et al.[46]	Implantable miniature telescope for end-stage AMD	United States	Sharma 2002, B Sharma 2000,[2 1999, Brown 20 Brown 2001, Br Nrown 2002
Patel et al.[47]	Bevacizumab for AMD	United States	Modified from E
Kim et al.[22]	PDT for AMD	Korea	Within study (E
Neubauer et al.[48]	Ranibizumab for nAMD	Germany	Brown 2000[10]
Hodge et al.[49]	Pharmacologic management of nAMD	Canada	Sharma 2000[25
Neubauer et al.[50]	Retinal pigment epithelium and choroid translocation for nAMD	Germany, United States	Bansback 2007[
Grieve et al.[51]	Verteporfin PDT for nAMD	United Kingdom	Within study (SI
Gower et al.[52]	Pegaptanib and ranibizumab for nAMD	United States	Brown 2002, Br
Hernandez-Pastor et al.[53]	Ranibizumab for nAMD	Spain	Brown 2000[10]
Karnon et al.[54]	Screening for AMD	United Kingdom	Espallargues 20 2000[10]
Fletcher et al.[55]	Treatments for nAMD	Not specified	Sharma 2000[25
Hurley et al.[56]	Smoking cessation to prevent AMD	United States	Brown 2000[10]

Hurley et al.[57]	Ranibizumab for nAMD	United States	Brown 2000[10
Bojke et al.[58]	Screening for AMD	United Kingdom	Brown 2001[59
Javitt et al.[60]	Early treatment of AMD with pegaptanib	United States	Brown 2000[10
Earnshaw et al.[61]	Pegaptanib for AMD	Canada	Brown 2000[10
Brown et al.[62]	Ranibizumab for AMD	United States	Brown 2001[59
Wolowacz et al.[63]	Pegaptanib for AMD	United Kingdom	Brown 2000[10
Raftery et al.[64]	Ranibizumab for AMD	United Kingdom	Brown 2000[10
Brown et al.	Interventions for AMD	United States	Brown 2001[59
Rein et al.[65]	Vitamin therapy for AMD	United States	Brown 2003
Bansback et al.[66]	Verteporfin PDT for AMD	United Kingdom	Espallargues 20
Brown et al.	Verteporfin PDT for nAMD	United States	Brown 2001[59
Sharma et al.[67]	anecortave acetate for AMD	Not specified	Within study (T
Trevithick et al.[68]	Vitamin therapy for AMD	Canada	Not specified
Smith et al.[69]	Verteporfin PDT for AMD	United Kingdom	Brown 2000[10
Hopley et al.[70]	Verteporfin PDT for nAMD	Australia and United Kingdom	Brown 2000[10
Hopley et al.[71]	Screening and zinc/antioxidants for AMD	Australia and United Kingdom	Sharma 2000[25
Busbee et al.[72]	Laser photocoagulation	United States	Brown 1999
Meads et al.[73]	Verteporfin PDT for AMD	United Kingdom	Brown 2000[10
Sharma et al.[74]	Verteporfin PDT for AMD	United States	Brown 2000[10
Brown et al.[75]	Laser photocoagulation	United States	Brown 1999
NICE TA298	Ranibizumab for treating choroidal neovascularisation associated with pathological myopia	United Kingdom	Czoski Murray 2
NICE TA294	Aflibercept for wet AMD	United Kingdom	VIEW 2 study (E Brown 2007[62] 2010[52].
NICE TA155	Ranibizumab and pegaptanib for AMD	United Kingdom	Czoski Murray 2 Espallargues 20 2000[10]
NICE TA68	PDT for AMD	United Kingdom	Brown 2000[10
CADTH 2009	Pharmacologic management in nAMD	Canada	Sharma 2000[25

*ordered by year of publication.

Appendix

A1. References for papers identified in the review

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